

From the
INTERNATIONAL SEARCHING AUTHORITY

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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/US2004/032933

International filing date (day/month/year)
07.10.2004

Priority date (day/month/year)
10.10.2003

International Patent Classification (IPC) or both national classification and IPC
C12N5/06

Applicant
LIU, Ge Ming

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



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**WRITTEN OPINION OF THE
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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
☐ a sequence listing
☐ table(s) related to the sequence listing
 - b. format of material:
☐ in written format
☐ in computer readable form
 - c. time of filing/furnishing:
☐ contained in the international application as filed.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

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Box No. II Priority

1. ☐ The following document has not been furnished:

- ☐ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).
- ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. ☒ It has not been possible to consider the validity of the priority claim because a copy of the priority document was not available to the ISA at the time that the search was conducted (Rule 17.1). This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.
4. Additional observations, if necessary:

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 6, 11-15, 25-33, 44-56

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 6, 11-15, 25-33, 44-56

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

☐ has not been furnished

☐ does not comply with the standard

the computer readable form

☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

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Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:
- ☐ paid additional fees.
 - ☐ paid additional fees under protest.
 - ☒ not paid additional fees.
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
 - ☒ not complied with for the following reasons:
see separate sheet
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☐ all parts.
 - ☒ the parts relating to claims Nos. 1-5, 7-10, 16-24, 34-43

Box No. V Reasoned statement under Rule 43b/s.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	16-24
	No: Claims	1-5, 7-10, 34-43
Inventive step (IS)	Yes: Claims	
	No: Claims	1-5, 7-10, 16-24, 34-43
Industrial applicability (IA)	Yes: Claims	1-5, 7-10, 19-24, 34-43
	No: Claims	16-18 (reserved opinion)

2. Citations and explanations
- see separate sheet**

III. NON-ESTABLISHMENT OF OPINION

- 1) **Claims 16-18** relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

For the assessment of the present **Claims 16-18** as far as they are directed to a method of treatment of the human or animal body or to a diagnostic method practised on the human or animal body, no unified criteria exist in the PCT, on the question whether they are industrially applicable. The patentability can be dependent upon the formulation of the claims.

- 2) As a result of lack of unity, only the first invention mentioned in the claims has been searched covering **Claims 1-5, 7-10, 16-24, 34-43**. In accordance with Article 34 (3)(c) PCT and Rule 66.1(e) PCT, no preliminary examination report shall be established for parts of the application that have not been searched.

IV. LACK OF UNITY OF INVENTION

- 3) The application as filed is considered to lack unity of invention since its subject-matter relates not to one but rather to two separate inventions not linked together by a common underlying inventive concept as required by Art. 3(4)(iii) PCT and Rule 13 PCT.
- 4) The claims and the inventions to which the four separate inventions relate may be grouped as follows:

INVENTION I

Claims 1-5, 7-10, 16-24, 34-43: A method for in vitro culturing of corneal epithelial cells; cells produced by said method; a method for transporting said cells; a method for storing target tissue that received said cells;

INVENTION II

Claim 6: A method for producing plates coated with extracellular matrix.

INVENTION III

Claims 11-13: An apparatus for growing cells in culture coated with bovine corneal endothelial cell extracellular matrix.

INVENTION IV

Claims 14-15: An apparatus for growing cells in culture coated with artificial extracellular matrix.

INVENTION V

Claims 25-33: A cell depository comprising human corneal endothelial cells; a method for producing said depository.

INVENTION VI

Claims 44-49: A method for denuding a cornea.

INVENTION VII

Claims 50-56: A preparation of a reconstituted extracellular matrix .

- 5) According to Rule 13 PCT, an international patent application must relate to one invention only or to a group of inventions so linked as to form a single general inventive concept. Unity of invention is fulfilled only when there is a technical relationship among the inventions involving one or more of the same or corresponding special technical features. Special technical features are such features that define the contribution of the claimed invention over the prior art.

The identified 7 inventions relate to various methods and products of culturing and maintaining corneal endothelial cells for transplantation, wherein said methods and products involve the technical feature of "culture of corneal endothelial cells in the presence of extracellular matrix components" as the sole common link. However, this feature cannot be accepted to constitute a special technical feature because it does not define a contribution over the prior art. Methods for *in vitro* culture of corneal endothelial cells involving extracellular matrix components are widely-known in the art (see the cited documents, for example, Ophthalmologie, (1999) vol. 96, p. 555-562; Cornea (2001), vol. 20, p. 59-63).

- 6) The contributions claimed in the present application which are allegedly made over the prior art are:

a) growing corneal endothelial cells on extracellular matrix and growth factors;

- b) seeding bovine corneal endothelial cells to produce the extracellular matrix;
- c) coating an apparatus with bovine corneal endothelial cells;
- d) coating an apparatus with artificial extracellular matrix;
- e) obtaining human corneal endothelial cells from donors;
- f) adding denuding reagent to immobilized corneal button;
- g) adding a combination of adhesion factors and growth factors.

These contributions represent the solution to several different and unrelated technical problems. Therefore, there is no single unifying inventive concept underlying the entire group of claims of the present application as required by Art. 3(4)(iii) PCT and Rule 13 PCT.

V. REASONED STATEMENT UNDER RULE 43bis 1(a) (i)

- 7) The following documents are referred to in the present communication:
 - D1: ENGELMANN K ET AL: "[Endothelial cell transplantation and growth behavior of the human corneal endothelium]" DER OPHTHALMOLOGE : ZEITSCHRIFT DER DEUTSCHEN OPHTHALMOLOGISCHEN GESELLSCHAFT. SEP 1999, vol. 96, no. 9, September 1999 (1999-09), pages 555-562.
 - D2: MIYATA K ET AL: "Effect of donor age on morphologic variation of cultured human corneal endothelial cells." CORNEA. JAN 2001, vol. 20, no. 1, January 2001 (2001-01), pages 59-63.
 - D3: DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; December 2002 (2002-12), AMANO SHIRO: "Transplantation of corneal endothelial cells." Database accession no. PREV200300187415.
- 8) The subject-matter of **Claims 1-5, 7-10, 34-43** relates to culturing corneal endothelial cells on plates coated with natural, produced by bovine corneal endothelial cells, or artificial extracellular matrix. The culture medium is further supplemented by growth factors. The method has been disclosed in documents D1-D3 and thus, said claims are not novel (Article 33(2) PCT).
- 9) The subject-matter of **Claims 16-24** relates to the generation of human corneal

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endothelial cells lacking class I HLA antigens. The application does not disclose such a method and thus, the inventiveness of said claims cannot be acknowledged (Article 33(3) PCT).

NB: The attention of the Applicant is drawn to the fact that a reply to this opinion is only expected if he intends to file a chapter II demand.